

DISCLOSURE OF CONFLICTS OF INTEREST

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19th Annual Congress

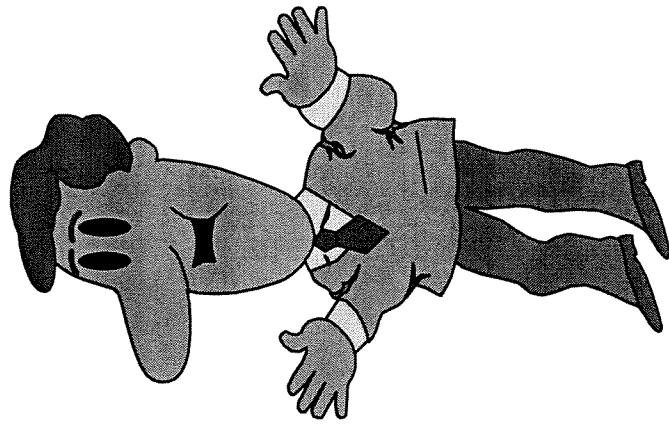
November 10-13, 2005, San Francisco, California

SESSION 7: FDA Evaluation Process of Foam Sclerosants

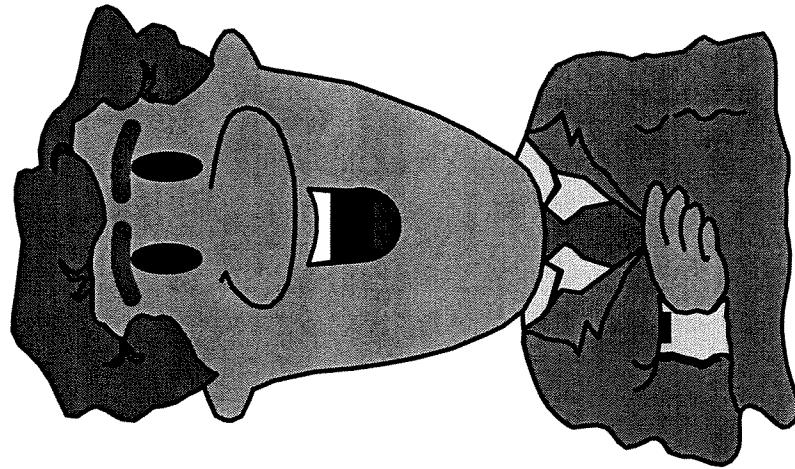
**I do not have any relevant financial relationships
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The opinions expressed here are not necessarily those of the FDA.



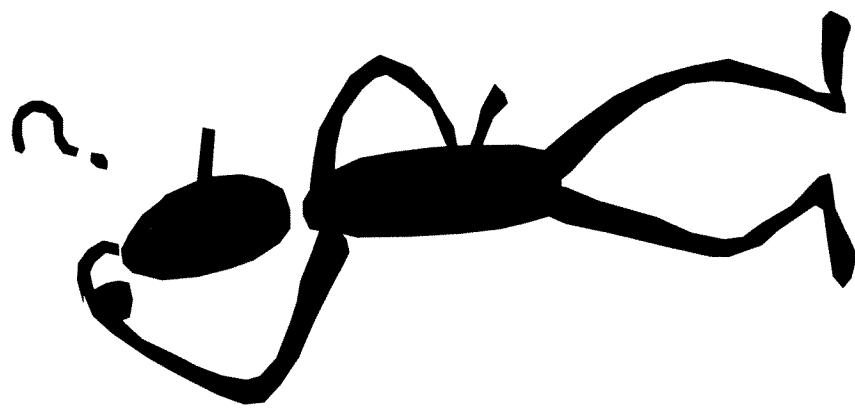
FDA Evaluation of Foam Sclerosants - What do we look for?



Safety!
Efficacy!



FDA Evaluation of Foam Sclerosants



**What is taking so long for the approval
of aethoxysklerol (polidocanol)?**

Reports of serious adverse events related to treatment of varicose veins with sclerosing agents

(ODS Reporting Period: Mar-2002 to Oct-2004)

Deaths

- 1 with aethoxysklerol (WHO)
- 4 with STS (US)

Serious Adverse Events

- 42 = Allergic reactions including 4 = anaphylactic shock (with aethoxysklerol)**
- 2 = Pulmonary Embolism (with STS)**

(These reporting systems typically under-report by a factor of 10 or more.)

Reports of serious adverse events related to treatment of varicose veins with sclerosing agents

(ODS Reporting Period: Mar-2002 to Oct-2004)

**Sclerosing agents can cause Serious Adverse Events (SAEs),
including deaths.**

These SAEs are probably rare - we don't know how rare.

**For approval, FDA needs better characterization of how frequently
these SAEs occur.**

Detect Effect of Foam Sclerosants on endothelium of:

- Large veins
- Endocardium
- Pulmonary artery
- {in patients with patent foramen ovale (PFO)}
cerebral circulation, hepatic and renal arteries

Detect Effect of Foam Sclerosants on endothelium of Large veins

**Duplex ultrasound of leg veins (microfoam is visible on
Doppler):**

Track intravascular trajectory of the microfoam

Detect Effect of Foam Sclerosants on the Heart

One recent (24-Mar-05) report:

A patient developed generalized seizures, incontinence of urine and apnea, had to be resuscitated, and was hospitalized for 1 week.

Reason = Cardiovascular problem

Detect Effect of Foam Sclerosants on the Heart

Transthoracic echocardiogram

At baseline:

R/o cardiomyopathy

Bubble study (+Valsalva maneuver) to detect Patent Foramen Ovale (population incidence $\approx 27.3\%$), ASD, ASA

Post-injection

To ensure foam is not flipping around in heart chamber

***12-Lead ECG**

At baseline, post-treatment and 24 hours

***CPK, CK-MB, Troponin T (2nd generation assay)**

At baseline, and q8H x 3

**If abnormal, monitor patient in hospital till resolved.*

Detect Effect of Foam Sclerosants on Brain

Detection of micro-infarcts in patients with microbubbles in MCA

Screening baseline neurological test and visual field test

- (1) One patient: tremors of right hand and dysgraphia.**
- (2) Two patients: visual disturbances (one had hypoesthesia)**
- (3) One patient: visual migranous aura and numbness of the other leg just after injection. Next sclerotherapy session cause the same symptoms.**

Symptoms and signs appeared a few minutes after injection, lasted a few hours, and recovered without sequelae.

Detect Effect of Foam Sclerosants on Brain

Detection of microbubbles in MCA

Transcranial Doppler (TCD)

- Non-invasive
- Can detect angiographic occlusions in MCA (>90%)
- Allows real-time readout of velocity changes in MCA

When?

- At baseline
- Throughout the procedure and for 1 additional hour

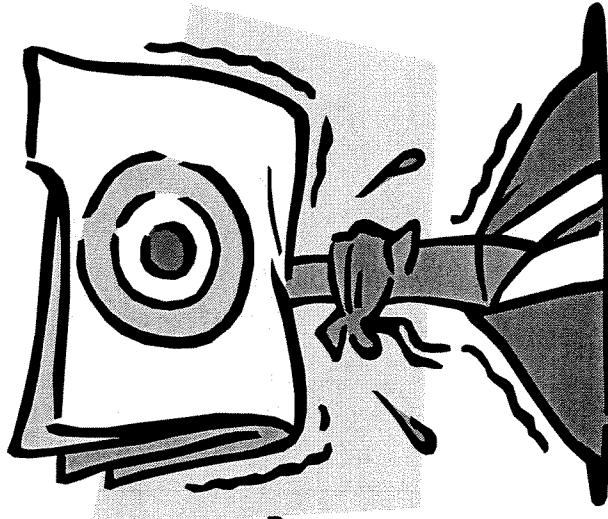
Subjects who are positive for microbubbles in MCA will have brain MRI's done.

Detect Effect of Foam Sclerosants on Brain

Detection of micro-infarcts

Brain MRI's:

- T2 imaging
- Diffusion-Weighted Image MRI (DWI MRI),
and
- Perfusion Weighted Image MRI (PWI MRI)



Does deep vein thrombosis (DVT) occur with use of Foam Sclerosants?

YES.

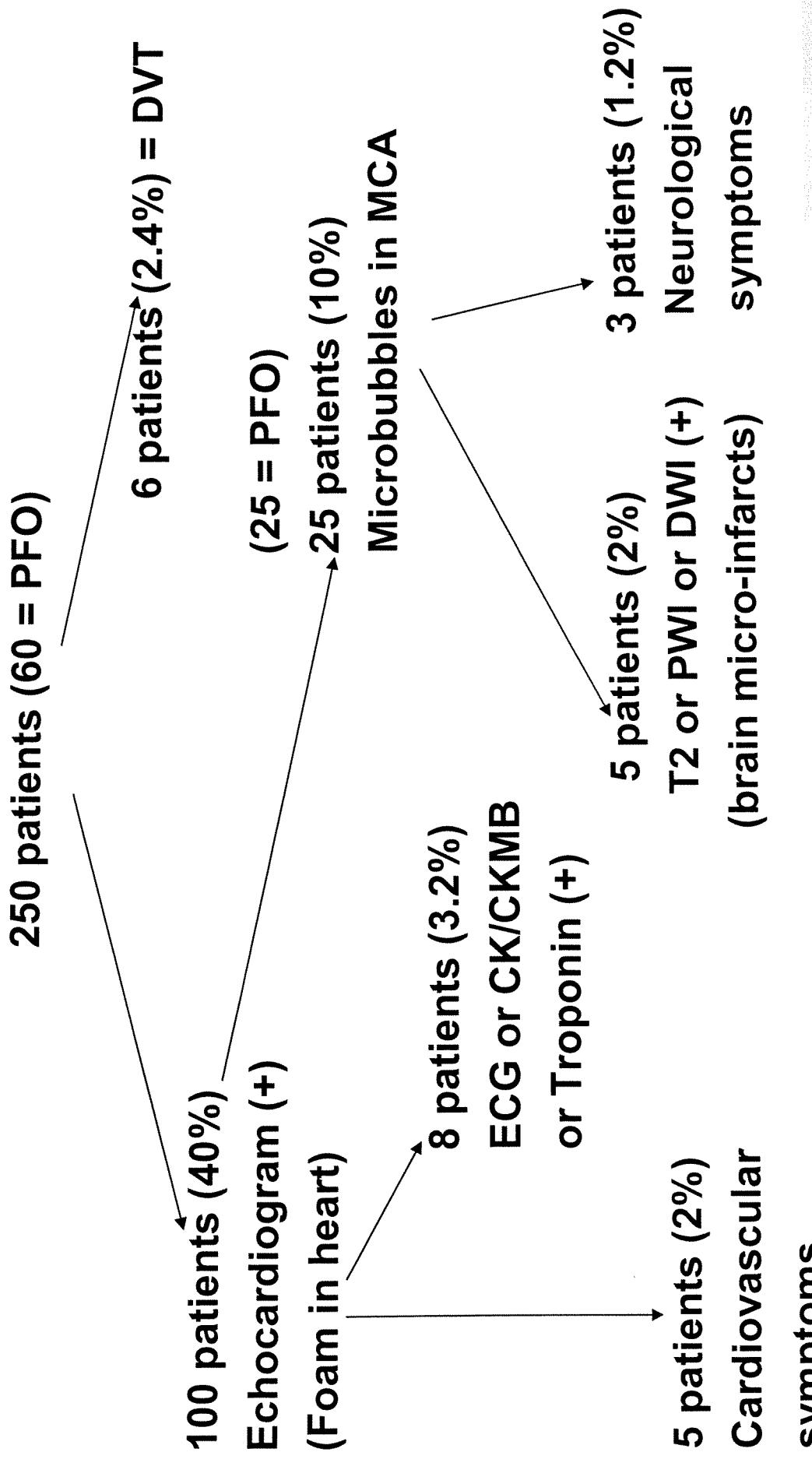
Four patients with DVT in peroneal muscle – (bilateral in one patient) – reported by one physician using 2% aethoxysklerol foam

Two patients reported by one physician (used aethoxysklerol 3% foam /1% liquid): one patient had antithrombin III defect and the other had heterozygous Factor V mutation.

Literature: Three cases of thrombus propagation in deep vein system following foam injection.

Safety Aspects of Foam Sclerosants

Hypothetical Characterization



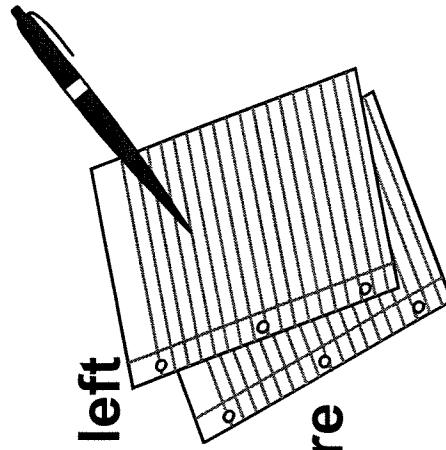
Efficacy Issues related to Clinical Trials of **Foam Sclerosants**

Standardize the disease:

Document the severity of varicose vein (e.g.,
CEAP1, 3, etc.)

Document where the vein to be treated is (e.g., left
or right leg)

Keep photographs or digital photographs or
digital images using a standardized procedure



MAINTAIN ALL RECORDS

Efficacy Issues related to Clinical Trials of Foam Sclerosants

Standardize the treatment:

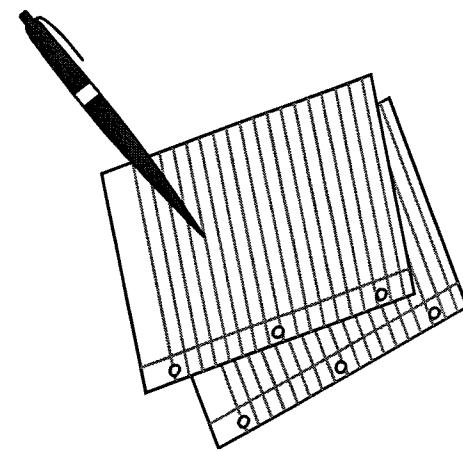
Dose: concentration, amount and volume

Administration: Ultrasound-guided injection

***In vitro* dose: bubble diameter, color of foam aspirate,
presence of venospasm**

Document ALL in CRFs

MAINTAIN ALL RECORDS





Efficacy Issues related to Clinical Trials of Foam Sclerosants

Specify the procedures:

- Randomization
- Blinding
- Statistical Plan



Efficacy Issues related to Clinical Trials of Foam Sclerosants

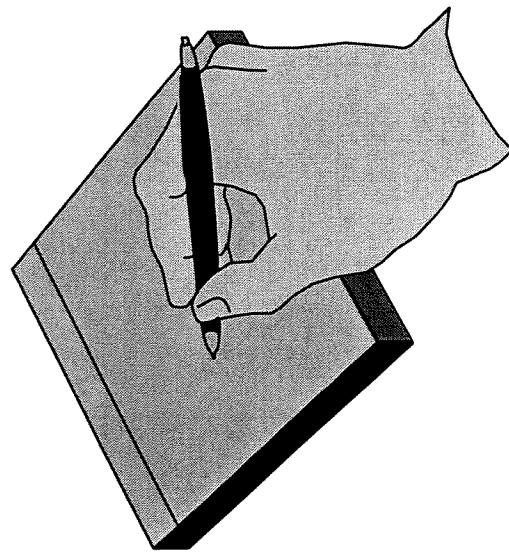
Standardize the efficacy endpoint (surrogate):

What? E.g., complete occlusion of varicose veins or disappearance of a spider vein

How? E.g., duplex ultrasound and spectral display or digital images or photographs

When? E.g., 28 days post-treatment

What is (are) the “clinical” endpoint(s)?



Drugs should result in ...

⌘ Feeling better

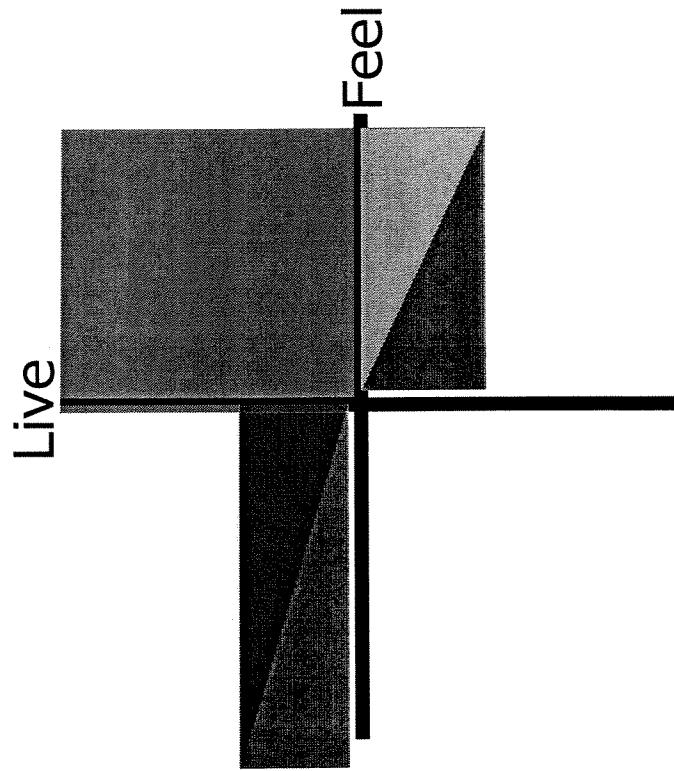
Functional status

Hospitalization, other therapy

Global assessment

⌘ Living longer

⌘ If you have to choose, then choice should make sense



**What is taking so long for the approval of
aethoxysklerol (polidocanol)?**

Efficacy!

Safety!

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